UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,285	03/16/2001	Connie M. Drysdale	MWH-0303US2	2691

25106 7590 11/24/2004

GENAISSANCE PHARMACEUTICALS
5 SCIENCE PARK
NEW HAVEN, CT 06511

EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,285	DRYSDALE ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8 and 29-33* is/are pending in the application.

4a) Of the above claim(s) *5,7,8,29,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-4, 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11122002 06212001* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, corresponding to SEQ ID NO: 21, in the reply filed 9/21/2004 is acknowledged. The traversal is on the ground(s) that the nucleic acid sequences are a Markush group and share unity of invention under In re Harnisch. This is not found persuasive because Harnisch requires that unity of invention exists when compounds included in the Markush group share a common utility, which is met here, but the sequences must also share a substantial structural feature disclosed as being essential to that utility,. Here the utility is detection of polymorphic variant of β2-AR. Applicant argues that each isogene has at least 523 nucleotides in common defining the substantial structural feature. However, the utility the sequences share, that of detecting polymorphic variants of β2-AR is not shared by the 523 nucleic acids in common, but by the nucleic acids which differ between the sequences. The variant nucleotides carry the utility for the group of nucleic acids, not the 523 nucleotides in common, since in order to detect polymorphic variants requires the use of the variant nucleotides, not the nucleotides in common. Thus, lacking the substantial structural feature being essential to that utility, the sequences lack unity of invention. Claims 5, 7-8, 29, 32-33 are withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 1, 3-4, 30-31 are under consideration.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The abstract of the disclosure is objected to because it is entitled "Abstract of the Invention". Pursuant to 37 CFR 1.72 a brief abstract of the technical disclosure in the

specification must commence on a separate sheet, preferably following the claims, under the heading "Abstract" or "Abstract of the Disclosure". Correction is required. See MPEP § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

Information Disclosure Statement

References BQ, BR, BS on the IDS submitted 11/12/2002 have been lined through because they are not in the correct format. The citation should include the author, pursuant to 37 CFR 1.98.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 4, 31 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims as written reads on a recombinant organism transfected with a nucleic acid. According to the Specification on page 13, this includes mammalian cells. As there is no limitation wherein the host cells are isolated, this claim reads on a transgenic human, which is not patentable subject matter.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a full length β2 adrenergic receptor encoded by the nucleic acid of SEQ ID NO: 21, does not reasonably provide enablement for a polymorphic variant of SEQ ID NO: 21. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are overly broad since insufficient guidance is provided as to which of the myriad of encoded variant polypeptides that will retain the characteristics of β2 adrenergic receptor. However, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible polymorphic variants of β2 adrenergic receptor. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome, and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of polymorphic variant sequences are not defined. Additionally, as an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function

of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. While the claims set forth a functional

limitation for the variant polypeptides wherein the polypeptide is capable of being activated by a β-agonist, the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polymorphic variants of β2AR, and has not taught how to make polymorphic variants of β2AR, it would require undue experimentation of one of skill in the art to make and use the claimed nucleic acids.

Claims 1, 3-4, 30-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO: 21 and therefore the written description is not commensurate in scope with the claims drawn to polymorphic variants of a DNA molecule comprising a DNA sequence of SEQ ID NO: 21.

The claims are drawn to polymorphic variants of SEQ ID NO: 21. These are genus claims, because the claims are directed to variant polynucleotides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claims do not place any limit on the number of substitutions, deletions, insertions and/or additions that may be made to the β2AR variants. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 21 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Stratagene (1991).

The Stratagene catalogue teaches the use of random 9-mers capable of hybridizing to all gene sequences. The random primers meet the limitations of claim 1 in that said primers are isolated DNA complementary to a sequence set forth in SEQ ID NO: 21.

Claims 1, 3-4, 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Emorine et al. (1987).

The Emorine reference teaches the isoltation of the genomic gene coding for the human beta 2-adrenergic receptor (beta 2AR). The reference further teaches transfection of the gene into eukaryotic cells restores a fully active receptor/GTP-binding protein/adenylate cyclase complex with beta 2AR properties. This reference anticipates the claims because the polynucleotide is complementary to SEQ ID NO: 21, is in an expression vector, and is expressed in host cells.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JOSEPH MURPHY
PATENT EXAMINER

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
November 18, 2004